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Reference

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Does delayed gastric emptying really cause symptoms in functional dyspepsia? We still doubt it!

We enjoyed reading the provocative commentary by Camilleri (*Gut* 2006;55:909–10) on our large study of patients with functional dyspepsia (*Gut* 2006;55:933–9). We completely agree that delayed gastric emptying is a marker of disturbed pathophysiology in functional dyspepsia; indeed, we first reported this observation in 1989.¹ However, we remain unconvinced, based on the available data, that this abnormality alone is linked to upper gastrointestinal symptoms.^{1–3} Factor analysis studies from the general population, in the absence of objective testing, do not provide insights into this issue,^{4,5} although we have shown that non-consulters with dysmotility-like dyspepsia are more likely to have gastric emptying delay.⁶ Studies from selected tertiary care patients are of interest, but Camilleri has previously reported negative results.³ Importantly, in a previous study of 551 patients with functional dyspepsia and 247 patients with type I diabetes and postprandial dyspepsia, gastric emptying, as measured by C¹³ octanoic acid breath testing, was also not linked to any specific upper gastrointestinal tract symptomatology.²

Interpretation of the symptom associations identified does need clarification, as statistical significance in a large study does not equate with clinical relevance. Our primary goal was to determine whether delayed gastric emptying was inducing symptom disturbances that, in turn, impair quality of life. The results from the models clearly suggest that while symptoms are associated with impaired quality of life in functional dyspepsia, gastric emptying is, at best, a very minor contributor and arguably has little clinical relevance.

We therefore dispute the view that there is overwhelming evidence of an association between symptoms and delayed gastric emptying. Indeed, we would argue that there continues to be accumulating evidence that there is often a disconnection between symptoms and slow gastric emptying. This does not negate the fact that delayed gastric emptying is an important biomarker, but it does strongly suggest that the symptom experience is related to other key factors that remain to be accurately identified.

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Author's reply

The first demonstration of impaired gastric emptying in functional dyspepsia should be attributed to Rees and colleagues.¹ Additional information provided does not specifically counter the solid arguments offered in the commentary.

In response to the points raised I would like to put forth the following.

Firstly, the reason for dismissing in the published study a positive and significant association between postprandial fullness and gastric emptying is still not provided and appears arbitrary.

Secondly, reference number 2 (Talley *et al* 2001) in the letter was also an observational study of patients with functional dyspepsia and postprandial diabetic dyspepsia (clearly different conditions) participating in a multi-centre drug study using a stable isotope gastric emptying test. The latter was subsequently shown to require more sophisticated mathematical analysis to provide accurate estimates of gastric emptying.^{2,3} As the gastric emptying data in reference number 2 (Talley *et al* 2001) are suspect, they cannot be used to support the claim that gastric emptying does not contribute to symptoms.

Thirdly, the strongest observational data in functional dyspepsia are in the approximately 800 consecutive patients diagnosed and studied in a uniform manner at a single centre by Tack and colleagues.⁴ In this study, a significant association between gastric emptying delay and symptoms of early satiety, nausea, vomiting, and fullness was convincingly demonstrated. It is possible that

discrepancies between the studies may reflect the wide spectrum of patients included under "epigastric pain and discomfort" in the Rome I and II criteria for dyspepsia. The reference to Bredenoord *et al* (reference No 3 in the letter) is quoted out of context as that study had a different aim, and symptoms were evaluated by patient history rather than in response to a standardised meal.

Fourthly, my commentary never claimed that there was overwhelming evidence that gastric emptying alone was responsible for symptoms. Rather, the literature (summarised in Tack's review⁴) shows that combinations of symptoms (typically those now grouped in the "postprandial distress syndrome" in the Rome III criteria for functional dyspepsia⁵) are associated with abnormal gastric functions, including abnormal gastric emptying.

Controlled perturbations of physiology provide a more meaningful appraisal of the causative relationship between pathophysiology and symptom generation. Abnormal gastric emptying is not just a biomarker. Our studies show that several physiological perturbations (for example, gastric emptying, sensitivity, and dysaccommodation) also contribute to the variance in symptoms.⁶ In studies to date, no single factor has explained more than 25% of the variance in symptoms of patients with dyspepsia.⁶ However, this does not justify dismissal of gastric emptying as a causative cofactor in dyspepsia.

The statement that "gastric emptying has arguably little clinical relevance" by Talley *et al* is not based on a fair global interpretation of the available literature.

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Association of tumour necrosis factor α promoter haplotype with chronic pancreatitis

Genetic risk factors are attributed an important role in the pathogenesis of chronic pancreatitis.¹ The genetic basis of chronic pancreatitis is complex. The cationic trypsinogen gene,² serine